UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

ILLUMINA, INC., et al.,

Plaintiffs,

v.

BGI GENOMICS CO., LTD, et al.,

Defendants.

Case No. 19-cv-03770-WHO

ORDER RE MOTIONS FOR PRELIMINARY INJUCTIONS

Before me are two motions for a preliminary injunction filed by plaintiffs Illumina Inc. and Illumina Cambridge Ltd. (collectively, "Illumina") in two related cases before me.[1] Illumina contends that defendants BGI Genomics Co., Ltd., BGI Americas Corp., MGI Tech Co., Ltd., MGI Americas, Inc., and Complete Genomics, Inc. (collectively, "BGI") infringe five of its patents related to DNA sequencing in two sets of its products. I find that Illumina has established a likelihood of infringement in both cases. Moreover, BGI has failed to identify significant questions as to the validity of Illumina's patents, several of which have been challenged and found to be valid in the past. I further find that Illumina would suffer irreparable harm as a result of BGI's infringing activities. For these reasons, and because the balance of equities weighs in favor of an injunction, Illumina's motions are GRANTED.

BACKGROUND

I. FACTUAL BACKGROUND

Illumina is a market leader in the field of sequencing deoxyribonucleic acid ("DNA"), and specifically in a method known as sequencing-by-synthesis ("SBS"). *Illumina I*, Dkt. No. 1 ("Compl.") ¶¶ 1, 36. DNA is comprised of two strands of molecules called nucleotides that take

[1] These two cases are Case No. 19-cv-3770 ("*Illumina I*") and Case No. 20-cv-1465 ("*Illumina II*").

the form of a double helix. *Illumina I*, Dkt. No. 84-4 ("Mot. I") at 3-4. Every nucleotide consists of a sugar molecule and a phosphate molecule, which form the backbone of each DNA strand, and a chemical base, which binds with a complementary chemical base in the other strand (often described as the "rung" of the DNA "ladder"). *Id.* The chemical base may be one of four molecules: adenine, guanine, cytosine, and thymine. *Id.* Each one of these molecules binds or pairs with only one other molecule; for example, guanine only pairs with cytosine and adenine only pairs with thymine. *Id.* at 5.

SBS uses this basic complementary pairing principle in order to sequence unknown DNA molecules. *Id.* at 4. It is possible to determine the sequence of one strand of a DNA molecule to be sequenced, often called target DNA, by identifying the sequence of the complementary nucleotides that bind with it. *Id.* In SBS, nucleotides are "incorporated" or bound to the target DNA strand and "read" one by one. *Id.* In other words, nucleotides are added one at a time to bind with a complementary nucleotide base in the target DNA strand, and each time a nucleotide is added it is identified as adenine, guanine, cytosine, or thymine. *Id.* at 4-5. In this way, it is possible to determine the sequence of the target DNA strand.

Illumina's patents specify several aspects of SBS, and in particular the method of adding nucleotides one at a time so that each one can be read before another nucleotide is added. *See id.* at 6-8. Illumina's patents describe a process by which target DNA is first immobilized upon a surface (such as glass) and treated with a sequencing primer. *Id.* at 5. Next, an enzyme is added that can help catalyze the incorporation of a new nucleotide to the target strand. *Id.* Then, nucleotides are added as described above so that they can be incorporated and identified.

The nucleotides that are added to the target DNA strand are part of Illumina's patented technology and the subject of some of the claims at issue. Each nucleotide contains a "blocking group," also known as a "protecting group," that prevents the next nucleotide from binding to the target DNA strand. *Id.* at 6. This blocking group is removable, however, so that once the nucleotide is read it can be removed and the next nucleotide incorporated. *Id.* Some of Illumina's patents also claim nucleotides that contain "detectable labels" that allow the reading of each nucleotide. *Id.* Thus, every nucleotide may contain a protecting group and a detectable label that

facilitate the process of reading the DNA strand one nucleotide at a time. One of the primary inventive features of Illumina's patents is the use of azidomethyl groups as the "blocking group" used in the SBS process. *Id.* at 1.

II. PROCEDURAL BACKGROUND

One of Illumina's patents at issue, U.S. patent number 7,566,537 (the "'537 patent"), was previously the subject of several proceedings in federal court and before the Patent Trial and Appeals Board ("PTAB"). In 2013, Intelligent Bio-Systems, later acquired by Qiagen N.V. ("Qiagen"), instituted an *Inter Partes Review* ("IPR") before the PTAB that challenged the '537 patent on obviousness grounds. *Illumina, Inc. v. Qiagen, N.V.*, 207 F. Supp. 3d 1081, 1086 (N.D. Cal. 2016). The PTAB instituted review based upon some of the references and upheld the validity of the patent. *Id.* Qiagen appealed to the Federal Circuit, which affirmed the decision. *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359 (Fed. Cir. 2016) ("*IBS*"). Illumina then sued Qiagen in this district for infringement of the '537 patent and sought a preliminary injunction, which the Hon. William H. Alsup granted. *Qiagen*, 207 F. Supp. 3d at 1086, 1094.

In 2017, CGI filed two IPR petitions challenging the '537 patent on grounds of obviousness. *Illumina II*, Dkt. Nos. 76-11, 76-12. The PTAB denied both petitions. *Id.* In 2019, BGI sued Illumina for infringement of its patents in the District of Delaware, which is ongoing. *Complete Genomics, Inc. v. Illumina, Inc.*, 1-19-cv-00970 (D. Del.).

Illumina filed the complaint in *Illumina I* on June 27, 2019. *Illumina I*, Dkt. No. 1. It alleges that BGI infringes U.S. patent number 9,410,200 (the "'200 patent") and the '537 patent by selling its sequencers and related reagents (collectively, "standardMPS"). *Id.* ¶¶ 2, 33-44. Illumina asserts that BGI's standardMPS sequencers, in particular BGISEQ-500, BGISEQ-50, MGISEQ-200, MGISEQ-2000, and MGISEQ-T7 (referred to as "BGISEQ" and "MGISEQ" devices) infringe claim 1 of the '537 patent and claim 1 of the '200 patent. *Id.* ¶ 35. BGI has agreed not to sell these sequencers in the United States pending this decision on Illumina's motion for preliminary injunction. *Illumina II*, Dkt. No. 11 ("Mot. II") 14.

Illumina filed the complaint in *Illumina II* on February 27, 2020, after it learned of a new

product developed by BGI called CoolMPS™ ("CoolMPS"). *Illumina II*, Dkt. No. 1. In the second lawsuit, Illumina asserts infringement of U.S. Patent numbers 7,771,973 (the "'973 patent"), 7,541,444 (the "'444 patent"), and 10,480,025 (the "'025 patent"). *Id.* ¶ 2. The '973, '444, and '537 patents claim priority to or are a divisional of the same patent application. *Id.* ¶ 38. Illumina claims BGI's CoolMPS products, which are purportedly based upon new sequencing chemistry, infringe claim 13 of the '973 patent, claim 3 of the '444 patent, and claim 1 of the '025 patent. *Id.* ¶¶ 48, 65, 146, 232. BGI has announced its intent to launch CoolMPS commercially in the United States, unlike standardMPS. *Id.* ¶ 48.

Illumina filed a motion for preliminary injunction in *Illumina I* on February 19, 2020**.** Mot. I. On February 27, 2020, the day that it filed the complaint in *Illumina II*, it filed its second motion for preliminary injunction. Mot. II. Thereafter, the parties agreed to file omnibus oppositions and relies on April 11, 2020 and April 27, 2020 to address the preliminary injunction motions in both cases. *Illumina I*, Dkt. No. 124-3 ("Opp."), Dkt. No. 137-4 ("Reply"). Over Illumina's opposition, I granted BGI's motion to submit a sur-reply to address new evidence presented in Illumina's reply that it was unable to address in its opposition due to scheduling restrains, which BGI submitted on May 4, 2020. *Illumina I*, Dkt. Nos. 142, 146. I heard this matter on May 11, 2020. *Illumina I*, Dkt. No. 156. After the hearing, the parties each filed supplemental submissions. *Illumina II*, Dkt. Nos. 95, 97.

LEGAL STANDARD

A plaintiff seeking a preliminary injunction must establish four factors: (i) that he is likely to succeed on the merits, (ii) that he is likely to suffer irreparable harm in the absence of preliminary relief, (iii) that the balance of equities tips in his favor, and (iv) that an injunction is in the public interest. *Apple Inc. v. Samsung Elecs. Co.*, 695 F.3d 1370, 1373–74 (Fed. Cir. 2012).

DISCUSSION

I. LIKELIHOOD OF SUCCESS ON THE MERITS

A. Infringement

BGI does not meaningfully dispute that its standardMPS products accused in *Illumina I* infringe Illumina's patents. As Illumina asserted in its opening brief, "[i]n their discovery

response in this case regarding their position on infringement, Defendants did not deny that the use of their accused reagent kits use are covered by Illumina's [']537 and [']200 Patents." Mot. I 14; *see also* Dkt. No. 84-16 at 6-7 (denying infringement based on lack of use in United States). BGI does not address this argument in opposition, but instead argues that CoolMPS, which is accused in *Illumina II*, does not infringe Illumina's asserted patents. Opp. 5. Therefore, I find that Illumina has demonstrated a likelihood that BGI's standardMPS products infringe the '537 and '200 patents.

With respect to CoolMPS, Illumina argues that BGI "admit[s] that CoolMPS uses 'nucleotides with a 3'-O-azidomethyl blocking group' for sequencing, which is covered by Illumina's '444 and '973 Patents," and cites the declaration of its expert, Dr. Burgess. Mot. II 15. BGI disagrees, as discussed below.

1. Claim 13 of the '973 patent

First, BGI contends that Illumina improperly conflates the language of claim 13 requiring removal of the blocking group before "introduction" of the next nucleotide, as opposed to "incorporation" of the next nucleotide. Opp. 5. Claim 1, from which claim 13 depends, describes "[a] method for determining the sequence of a target single-stranded polynucleotide, comprising monitoring the sequential incorporation of complementary nucleotides. . ." *Illumina II*, Dkt. No. 1-1 ("'973 patent") 86:24-26. Its final limitation requires that "the blocking group is removed prior to introduction of the next complementary nucleotide." *Id.* 86:55-56. BGI argues that CoolMPS does not satisfy claim 13 of the '973 Patent "because CoolMPS can introduce the next batch of nucleotides to the reaction mixture *before* removal of the blocking group (D16 at 5-7), which is contrary to the actual claim language." Opp. 5.

This dispute turns on construction of the term "prior to introduction," and whether CoolMPS operates in a way that would not infringe under BGI's construction. The focus of the patent is on the use of a blocking group to prevent new nucleotides from binding. *See generally* Background. There is no significance in the patent in introducing new nucleotides before or after removal of the blocking group. The patent does not describe precisely when the blocking group should be removed or that removal must occur before "introduction" (in addition to before

incorporation) of new nucleotides. Instead, the claimed invention focuses on removal of the blocking group after the nucleotide is read, so that a new nucleotide may then incorporated to the strand and read in turn. Ultimately, BGI's argument is grounded less in the patent claims and specification, and more in the differences between the two words. While it is true that different terms in the patent are presumed to have different meanings, BGI's construction of the term would import a limitation into the patent claim that is not supported by anything in the patent specification.

In its supplemental reply brief, BGI argues that the claimed method involves a separate step of bringing nucleotides in contact with the growing strand. *Illumina II*, Dkt. No. 95-2 at 2. This portion of the specification, which is also the subject of a separate claim in the patent, does not use the term "introduction" but instead states that nucleotides are "brought into contact with the target." *See* '973 patent 6:19-24, 88:1-12. Moreover, this passage does not support BGI's position, because it contemplates nucleotides being "brought into contact with the target" before the blocking group is removed, which is what BGI contends that CoolMPS does. *See id.* 6:21-24 ("a composition comprising all of the different nucleotides is brought into contact with the target, and non-incorporated nucleotides are removed prior to detection and subsequent to removal of the label and the blocking group"), *see also id.* 6:16-24. 38-49. There is no support in the specification for BGI's narrow construction of the term "introduction."

BGI also points to several instances in the patent specification where molecules are "introduced" to a mixture of salts. Dkt. No. 95-2 at 2. But these citations relate to a different aspect of the invention. '973 patent 9:23-67. By contrast, when the specification discusses "introduction" of nucleotides it uses the term in a way very similar to, if not interchangeably with, the word "incorporation." *See id.* 4:47-55 ("the incorporation of said molecule *preventing or blocking introduction of subsequent nucleoside* or nucleotide molecules into said growing complementary polynucleotide") (emphasis added).

Finally, the actual operation of CoolMPS as argued by BGI does not show non-infringement even using its construction of "introduction." BGI claims that CoolMPS products "introduce" nucleotides that are used to remove fluorescently labeled antibodies—but not intended

to bind with the target strand—to the target DNA strand before the blocking group is removed. *See Illumina II*, Dkt. No. 95-2 at 4. After these nucleotides are used to remove the antibodies, CoolMPS then removes the blocking group before "introducing" the next nucleotide that is intended to be incorporated into the strand. *Id.* at 5; *see also Illumina II*, Dkt. No. 95-3 ¶¶ 19-20. Thus, while CoolMPS adds an additional step to the SBS process claimed in claim 13 of the '973 patent, it nonetheless practices every limitation of that claim.

Accordingly, Illumina has shown a likelihood that CGI infringes the '973 patent.

2. Claim 3 of the '444 patent

Claim 1 of the '444 patent provides for "[a] modified nucleotide molecule comprising a purine or pyrimidine base and a ribose or deoxyribose sugar moiety having a removable 3′-OH blocking group covalently attached thereto, such that the 3′ carbon atom has attached a group of the structure —O—Z wherein Z is any of" five enumerated structures. *Illumina II*, Dkt. No. 1-2 ("'444 patent") 85:65-86:36. It states:

—O-Z

wherein Z is any of —$C(R^{IV})_2$—O—R", —$C(R')_2$—N(R")$_2$, —$C(R')_2$—N(H)R", —$C(R^{IV})_2$—S—R" and —$C(R')_2$—N_3,

wherein —$C(R^{IV})_2$—O—R" is of the formula —$CR^4(R^5)$—O—$CR^4(R^5)$—OR^6 or of the formula —$CR^4(R^5)$—O—$CR^4(R^5)$—SR^6; and wherein —$C(R^{IV})_2$—S—R" is of the formula —$CR^4(R^5)$—S—$CR^4(R^5)$—OR^6 or of the formula —$CR^4(R^5)$—S—$CR^4(R^5)$—SR^6;

wherein each R" is or is part of a removable protecting group;

each R' is independently a hydrogen atom, an alkyl, substituted alkyl, arylalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclic, acyl, cyano, alkoxy, aryloxy, heteroaryloxy or amido group, or a detectable label attached through a linking group; or $(R')_2$ represents an alkylidene group of formula =$C(R'")_2$ wherein each R'" may be the same or different and is selected from the group comprising hydrogen and halogen atoms and alkyl groups;

each R^4 and R^5 is independently a hydrogen atom or an alkyl group;

R^6 is alkyl, cycloalkyl, alkenyl, cycloalkenyl or benzyl; and

wherein said molecule may be reacted to yield an intermediate in which each R" is exchanged for H, which intermediate dissociates under aqueous conditions to afford a molecule with a free 3'OH; with the proviso that where Z is —$C(R^{IV})_2$—S—R", both R^{IV} groups are not H.

Claim 3 states, in its entirety, "[a] molecule according to claim 1 wherein Z is an azidomethyl group." *Id.* 86:39-40.

The dispute between the parties centers on the final clause of claim 1 and whether it limits

claim 3. The final limitation in claim 1 recites that "said molecule may be reacted to yield an intermediate in which each R″ is exchanged for H, which intermediate dissociates under aqueous conditions to afford a molecule with a free 3′OH; with the proviso that where Z is —$C(R^{IV})_2$—S—R″, both R^{IV} groups are not H." '444 patent 86:31-35. BGI states that Illumina has not adequately shown infringement because it does not address the final limitation of claim 1. Opp. 6. Illumina primarily relies upon its expert to argue that where Z is an azidomethyl group, the final clause does not apply. Mot. II 15. Illumina's expert, Dr. Burgess, opined that an azidomethyl group satisfies the fifth enumerated structure in claim 1 (e.g., $C(R')_2$—N_3). *Illumina II*, Dkt. No. 13 ("Burgess Decl.") ¶ 42.

It is not immediately apparent whether the final clause of claim 1 must limit every enumerated "Z" structure or only applies to certain molecular configurations. Claim 1 clearly provides that R″ is or is part of a removable protecting group. '444 patent 86:14-15. Both parties agree that the an azidomethyl satisfies the fifth structure in claim 1, —$C(R')_2$—N_3, which does not contain a R″ and thus would not seem to implicate the final limitation, which requires a R″. At oral argument, BGI argued that azidomethyl also satisfies the second structure in claim one, —$C(R')_2$—$N(R'')_2$. While this is supported by the specification, claim 1 also provides for the more specific structure, — $C(R')_2$—N_3, in which —N_3 takes the place of $N(R'')_2$. *See id.* 12:16-21 ("One example of groups of structure —O—Z wherein Z is —$C(R')_2$—$N(R'')_2$ are those in which $N(R'')_2$ is an azido (—N_3). One preferred example is azidomethyl wherein each R′ is H. Alternatively, R′ in Z groups of formula —$C(R')_2$—N_3 and other Z groups may be any of the other groups discussed herein."). Moreover, the specification describes "the azido group in Z groups of formula $C(R')_2N_3$." *Id.* 12:64-65.

I find that Illumina has provided sufficient evidence to establish that the final clause of claim 1 does not apply to instances where "Z" is an azidomethyl, and thus that CoolMPS infringes this claim. The claim language and patent specification repeatedly describe an azido group as $C(R')_2$—N_3. Unlike the other enumerated structures in claim 1, there is no symbol for R″ in this structure, which indicates that the limitation regarding R″ does not apply to the azido structure. Illumina also provided expert testimony, which BGI does not rebut, that claim 1 is satisfied where

Z is azidomethyl. By contrast, BGI has not explained how an azidomethyl could satisfy the final clause of claim 1, and has not raised any enablement or indefiniteness argument with respect to this claim. *See Wright Med. Tech., Inc. v. Osteonics Corp.*, 122 F.3d 1440, 1445 (Fed. Cir. 1997) ("we must not interpret an independent claim in a way that is inconsistent with a claim which depends from it"); *see also Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) ("a dependent claim cannot be broader than the claim from which it depends.").

Therefore, I find that Illumina has satisfied its burden of establishing a likelihood of success on its argument that CoolMPS infringes the '444 and '973 patents.

B. Invalidity

The bulk of BGI's opposition briefing focuses on its arguments that the patents asserted in *Illumina II* are not valid. In such cases, "the burden is on the challenger [of a patent's validity] to come forward with evidence of invalidity, just as it would be at trial," and the patentee "then has the burden of responding with contrary evidence, which of course may include analysis and argument." *Titan Tire Corp. v. Case New Holland, Inc.*, 566 F.3d 1372, 1377 (Fed. Cir. 2009).

1. Enablement

"To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380 (Fed. Cir. 2012) (citations omitted). "Enablement serves the dual function in the patent system of ensuring adequate disclosure of the claimed invention and of preventing claims broader than the disclosed invention." *Id.* at 1380–81. In order to prove that a claim is invalid for lack of enablement, a challenger must show by clear and convincing evidence that a POSITA would not be able to practice the claimed invention without "undue experimentation." *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 13465(Fed. Cir. 2019). In analyzing whether an invention requires undue experimentation, the court considers "factors such as: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the

breadth of the claims." *Id.* (citation omitted).

BGI asserts that claim 13 of the '973 patent and claim 3 of the '444 patent are invalid for lack of enablement. First, it attacks the recitation of the term "nucleotide" in both patents because "each cover at least millions of 3'-O-azidomethyl blocked compounds." Opp. 8. It notes that at the time of the invention, there were thousands of sugar analogs, hundreds of detectable labels, and hundreds of cleavable or non-cleavable linkers, all of which are encompassed by the term "nucleotide." *Id.* at 8-9. Thus, "[e]ven a conservative estimate of this broad scope of 'nucleotide' encompasses millions of different 3'-O-azidomethyl nucleotides with different combinations of sugar and base analogs, detectable labels, and linkers." *Id.* at 9. It also takes issue with claim 13 of the '973 patent because it does not restrict the sequencing length of the target polynucleotide, and encompasses the use of any one of millions of enzymes to achieve incorporation. *Id.* at 9-10.

Next, BGI argues that the disclosures in both patents' specifications are insufficient. *Id.* at 10. The '444 patent specification describes the synthesis of only eight nucleotides, and making any other nucleotides would likely have been difficult. *Id.* at 10, 14. Moreover, the "specification of the '973 and '444 Patents describes no working example of using 3'-O-azidomethyl nucleotides in actual sequencing of a polynucleotide as recited in claim 13." *Id.* at 10-11. The specification of the '973 patent also "provides only generalized statements on how to make and use 3'-O-azidomethyl blocked nucleotides" and "is silent on how variables such as the base location, linker size and type, label size and type, and other modifications of nucleotides impact incorporation." *Id.* at 11-12. Moreover, "the specification of the '973 Patent provides no suggestion or teaching whatsoever on how to use *un*labeled nucleotides in sequencing methods, which is CGI's CoolMPS innovation." *Id.* at 12.

Illumina contends that BGI's challenge to the breadth of the patents is ill-founded because many of the challenged aspects of "nucleotides" with azidomethyl blocking groups are not actually claimed in either patent claim. Reply 5. With respect to claim 3 of the '444 patent, it states that "[t]he law requires a skilled artisan to be able to make the claimed composition, which is a single nucleotide modified to include an azidomethyl blocking group – not to produce every imaginable instantiation of the claim in some sort of mass synthesis project." *Id.* With respect to

claim 13 of the '973 patent, Illumina argues that the inventive aspect is the azidomethyl blocking group, and that the other elements that BGI discusses are unclaimed. *Id.* at 6. Moreover, it asserts that BGI effectively admitted that the invention was enabled in the prior IPR proceedings. *Id.* It states that the patent discloses a proper linker, label, and enzyme that a POSITA would understand. *Id.* at 6-7. Finally, claim 13 of the '973 patent requires the incorporation of only two bases, so the patent cannot fail for lack of enablement because of the difficulty in successfully reading long sequences. *Id.* at 8.

I start with the claims at issue; an enablement challenge pertains only to claimed aspects of the invention. *AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298–99 (Fed. Cir. 2014). And in establishing lack of enablement of a dependent claim, as with the claims here, BGI must demonstrate that the narrower dependent claim was not enabled, regardless of whether the independent claim from which it depends is not enabled. *Martek Biosciences Corp. v. Nutrinova, Inc.*, 579 F.3d 1363, 1378–79 (Fed. Cir. 2009).

The majority of BGI's arguments that the patents are invalid for lack of enablement stem from the breadth of the term "nucleotide" as used in both patents. However, "[p]recedent establishes that [t]he enablement requirement is met if the description enables any mode of making and using the invention," as "[c]ontinuing development is often contemplated and necessary, while early filing is often essential." *Edwards Lifesciences AG v. CoreValve, Inc.*, 699 F.3d 1305, 1309 (Fed. Cir. 2012) (citations omitted); *see also Takeda Pharm. Co. v. Zydus Pharm. USA, Inc.*, 743 F.3d 1359, 1369 (Fed. Cir. 2014) ("It is well established that the 'enablement requirement is met if the description enables any mode of making and using the invention.'").

Claim 3 of the '444 patent involves only a molecule, not a sequencing process. *See Illumina II*, Dkt. No. 76-5 ("Sutherland Dep.") 54:11-21. There is no dispute that the patent discloses at least one example of such a molecule. BGI and its expert admit that the specification of the '973 and '444 patents "provides the synthesis of only eight structurally similar molecules within the scope" of the claims, but argue that they "[do] not provide sufficient disclosure to make 3'-O-azidomethyl blocked nucleotides structurally divergent from those eight compounds." *Illumina II*, Dkt. No. 68-4 ("Sutherland Decl.") ¶ 49; Opp. 16. Indeed, BGI's expert repeatedly

stated that his concern with claim 3 was the breadth of the claim, not that a POSITA at the time would not have been able to make or use any iteration of the invention. Sutherland Dep. 164:6-23, 167:8-18, 169:5-13. Accordingly, BGI has not shown adequate evidence that claim 3 of the '444 patent is invalid for lack of enablement.

BGI's enablement argument with respect to claim 13 of the '973 patent largely also challenges the breadth of possible nucleotides that could be used in the invention. *See* Sutherland Dep. 166:3-168:19. As with claim 3 of the '444 patent, this argument fails because that is not the focus of the enablement inquiry; the focus is whether the patent would enable a POSITA to make and use the invention. Although BGI also challenges the '973 patent specification for failure to provide a working example of the method or to explain how certain variables impact incorporation or how to use unlabeled nucleotides, Opp. 10-11; Sutherland Decl. ¶¶ 52-58, it fails to tie these elements to the claimed invention or provide evidence that a POSITA would not be able to make or use the invention using the disclosed nucleotides without undue experimentation.[2] *See Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1339 (Fed. Cir. 2013) (party asserting enablement challenge "had the burden to show by way of testimony or documentary evidence the amount of experimentation needed" in order to show undue experimentation).

Judge Alsup rejected a similar argument in the *Qiagen* case. There, in challenging the '537 patent, Qiagen argued that the claims at issue were invalid because they "encompass[ed] a broad set of modified nucleotides that have a 'protecting group compris[ing] an azido group,' while an 'azido group' could refer to any of more than one thousand chemical groups." *Qiagen*, 207 F. Supp. 3d at 1092. Judge Alsup found that Qiagen did not identify even one inoperative combination and did not prove enablement. *Id.* The same issues are present here, and BGI has not established by clear and convincing evidence that a POSITA at the time would not have been able to practice any interaction of claim 13.

BGI relies heavily on *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340 (Fed. Cir. 2019). However, in that case the court focused on the unpredictability of the art at the

[2] BGI's arguments as to experimentation focus on the difficulty in identifying nucleotides other than those disclosed in the specification. Opp. 14-15.

time and the lack of an adequate description in the specification of any mode of using the invention. *Id.* at 1348. As discussed, I find that BGI has not shown that the description is inadequate. Moreover, although BGI contends that the state of the art at the time was highly unpredictable and novel, this argument is belied by the numerous previous proceedings involving Illumina's patents related to the same azido chemistry, where multiple challenges were brought based upon obviousness. Opp. 12-14; *see also* Reply 6. As Illumina points out, BGI previously contended that a POSITA would be able to practice various aspects of the invention that BGI now contends are not enabled. Reply 6-7. At base, BGI's objection to claim 13 is the breadth of the claim and the inability to identify alternative nucleotides to those disclosed in the patent, not the inability to practice the invention. Opp. 14 ("[M]aking new 3'-O-azidomethyl blocked nucleotides different than those eight nucleotides described in the specification would likely have been difficult."). Therefore, I find that BGI has failed to satisfy its burden of showing by clear and convincing evidence that the '973 patent is invalid for lack of enablement.

With respect to the patents asserted in *Illumina I*, BGI devotes only a cursory paragraph arguing that they are not enabled for the same reasons that the '973 and '444 patents are not enabled. Opp. 23. Because those arguments are unpersuasive, I reject BGI's argument that the asserted claims of the '025, '200, and '537 are not enabled.

2. Anticipation

"A determination that a patent is invalid as being anticipated under 35 U.S.C. § 102 requires a finding that 'each and every limitation is found either expressly or inherently in a single prior art reference.'" *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1375 (Fed. Cir. 2006). BGI contends that claim 3 of the '444 patent is anticipated by the "Zavgorodny"[3] prior art reference because it disclosed the same claimed blocking group on a nucleoside, while claim 3 describes a nucleotide. Opp. 18-20. BGI asserts that the terms "nucleoside" and "nucleotide" are interchangeable in the '537 and '444 patents, and thus the claim is anticipated. *Id.* Illumina counters that "nucleotide" and "nucleoside" are different terms because it is undisputed that a

[3] BGI cites two "Zavgorodny" references from 1991 and 2000, arguing that both anticipate claim 3. Opp. 18.

nucleoside lacks a phosphate group. Reply 9. This is significant because the patent examiner, when examining Zavgorodny, determined that claim 3 was patentable in part because it did not disclose nucleotides with phosphates. *Id.*

I am not persuaded by BGI's anticipation argument. The patent claims a nucleotide, not a nucleoside, and BGI's construction of the term is not reflected in the specification, which separately defines "nucleotide" and "nucleotide." *See* '537 patent 4:48-49 ("'nucleotide' consists of a nitrogenous base, a sugar, and one or more phosphate groups"), 4:59-60 ("A 'nucleoside' is structurally similar to a nucleotide, but are missing the phosphate moieties."). Rather, the specification reflects the commonly-understood distinction between the two terms (e.g., a nucleotide has a phosphate group and a nucleoside does not). As discussed in further detail below, the Zavgorodny reference has been extensively litigated with respect to the obviousness of the '537 patent, and no court has found that the patent was anticipated. Finally, as Illumina points out, the very argument that BGI now makes was presented to the patent office during the prosecution of the patent, and the current claim ultimately issued. *Illumina II*, Dkt. 58-34, Dkt. 58-38. Therefore, BGI has failed to show a substantial question that the '444 patent is invalid due to anticipation.

3. Obviousness

"A claim is invalid for obviousness if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." *Metalcraft of Mayville, Inc. v. The Toro Co.*, 848 F.3d 1358, 1366 (Fed. Cir. 2017) (citations omitted). Thus, a party challenging a patent on obviousness grounds must show that there would have been a motivation to combine prior art references to arrive at the claimed invention. *Id.*; *see also Forest Labs., LLC v. Sigmapharm Labs., LLC*, 918 F.3d 928, 934 (Fed. Cir. 2019) ("An invention is not obvious simply because all of the claimed limitations were known in the prior art at the time of the invention. Instead, we ask 'whether there is a reason, suggestion, or motivation in the prior art that would lead one of ordinary skill in the art to combine the references, and that would also suggest a reasonable likelihood of success.'").

BGI asserts that even if claim 3 of the '444 patent is not anticipated by the Zavgorodny references, it was nonetheless obvious in combination with other references. Opp. 20. It contends that "[a] POSITA would be motivated to convert Zavgorodny 1991's 3'-O-azidomethly blocked nucleosides into nucleotides for a variety of applications, including use in the studies of enzymatic reactions or organic chemistry." *Id.* at 21.[4] With respect to claim 13 of the '973 patent, BGI asserts that the combination of Zavgorodny and the "Parce" reference renders the claim obvious, because "Parce discloses a sequencing method using 3'-O-blocked nucleotides, which includes every claim 13 limitation except the 3'-O-azidomethyl blocking group." *Id.* at 22. A POSITA would have been motivated to replace the azidomethyl group in Zavgorodny for the blocking groups in Parce. *Id.* BGI relies upon the declaration of Dr. Sutherland and argues that it would be obvious to use an azidomethyl group in place of the blocking groups in the Parce reference because (i) Parce requires the use of TCEP for removal, which is "closely related to" a reducing agent disclosed in Zavgorodny and would be preferable for use with azidomethyl, and (ii) azidomethyl as disclosed in Zavgorodny is smaller and more stable than the blocking group used in Parce. Opp. 22-23; Sutherland Decl. ¶¶ 123-27. Further, BGI asserts that there was a reasonable expectation of success because similar molecules such as "AZT" were known to be incorporated by polymerases, Zavgorodny's disclosed azidomethyl would have been expected to block further incorporation, the disclosed azidomethyl would be expected to be removable using TCEP, and further incorporation of nucleotides would be possible after this azidomethyl was removed. Sutherland Decl. ¶¶ 129-32.

In response, Illumina points out that because Zavgorodny does not suggest sequencing, other parties have attempted—and failed—to show obviousness by combining Zavgorodny with other references that teach SBS. Reply 10. It also contends that such long-felt need confirms the previous findings of nonobviousness. *Id.* at 11-12.

I find that BGI has not adequately established that a POSITA would have been motivated

[4] BGI devotes a sentence in its brief (and one paragraph of Dr. Sutherland's declaration) to arguing that Zavgorodny combined with the "Haitt" reference renders claim 3 obvious. Opp. 21; Sutherland Decl. ¶ 113. This is not adequate to raise a substantial question of obviousness.

to combine Parce and Zavgorodny (or both Zavgorodny references) or that a POSITA would expect a reasonable likelihood of success. The argument that it would be obvious to use an azidomethyl group as taught by Zavgorodny with a variety of prior art references teaching sequencing has been extensively litigated and determined to be weak. *See IBS*, 821 F.3d at 1364–65 (noting that "the azidomethyl group would have been expected to perform inefficiently in that role" of a protecting group"); Dkt. No. 76-11 (April 20, 2018 IPR Board denial of petition to institute review of claims of '537 patent for obviousness); Dkt. No. 76-12 (April 20, 2018 IPR Board finding no reasonable likelihood of success in showing obviousness of '537 patent); *Qiagen*, 207 F. Supp. 3d at 1090.

BGI seeks to distinguish these decisions on the grounds that there was no motivation to combine Zavgorodny with the previously-litigated references that required high efficiency deblocking, because the Parse reference has no such requirement. *Illumina I*, Dkt. No. 145-3 at 4. Yet BGI also contends that azidomethyl would be "cleaved rapidly and efficiently in Parce's sequencing method," and is largely silent on how the lack of efficiency in Parce factors into its analysis of obviousness. Opp. 22; Sutherland Decl. ¶¶ 120-27. It is true that a focus of prior obviousness determinations hinged on quantitative (high efficiency) deblocking. But BGI has presented no evidence or argument to change the underlying determination in multiple prior decisions that "the ordinary artisan would have expected inefficient removal/deblocking of an azidomethyl moiety" in other prior art methods directed to SBS. Dkt. No. 76-12 at 11.

Moreover, a closer look at BGI's arguments confirms that the current obviousness argument is akin to those that have already been rejected by prior courts and the IPR Board. The Board examined a variety of prior art references in combination with Zavgorodny, and concluded it would not have been obvious to use azidomethyl in SBS methods. *See* Dkt. Nos. 76-11, 76-12 ("In using an azidomethyl protecting group in this way, the skilled person would not be exploiting an *advantage* of an azidomethyl group, but an expected *disadvantage*. We are not persuaded, absent hindsight, that the ordinarily skilled person would have done so — even in DNA sequencing applications with shorter-read lengths and where high efficiency deblocking is allegedly not as critical."). The Board rejected the argument that "it would have been obvious to

use TCEP . . . as the reducing agent" in a prior art reference due to concerns about DNA degradation. Dkt. No. 76-13 at 30-35. It also rejected similar arguments that the small size of azidomethyl or understanding of AZT would motivate a POSITA to use azidomethyl in combination with SBS methods taught in prior art references. *Id.* Finally, as Illumina points out and the prior cases reflect, long-felt need to identify suitable blocking groups for SBS confirms that the use of the Zavgorodny reference in connection with prior art directed to sequencing was not obvious. Reply 11-12; *see also Endo Pharm. Inc. v. Actavis LLC*, 922 F.3d 1365, 1377 (Fed. Cir. 2019) (non-obviousness "supported by the fact that the inventors of the [] patent engaged in extensive experimentation, involving much failure, to ultimately produce the [the molecule] of the Asserted Claims").

For these reasons, I find that BGI has not demonstrated a substantial question as to the invalidity of Illumina's patents with respect to obviousness.

4. Summary

Illumina has established a likelihood of success on the merits of its infringement arguments in *Illumina I* and in *Illumina II*. BGI has failed to raise a substantial question of invalidity. Accordingly, this factor weighs in favor of granting Illumina's motions.

II. IRREPARABLE HARM

To establish that it is likely to suffer irreparable harm, Illumina must establish likely harm and that there is a causal nexus between the alleged infringement and the alleged harm. *Metalcraft*, 848 F.3d at 1368. Lost sales alone will not suffice to establish irreparable harm; Illumina must show that "no amount of monetary damages, however great, could address the harm." *Id.*

BGI asserts that Illumina has failed to establish irreparable harm because it will launch only two products in the United States that will compete with only two of Illumina's six systems and that are not approved for clinical use in the U.S. Opp. 24. BGI also states that it is a new competitor and its revenue will be very low for the first few years after entry. *Id.* at 24-25. Further, it disputes Illumina's assertion that there will be price erosion, especially considering Illumina's practice of using long-term contracts and sole-source tenders. *Id.* at 25-26. BGI

contends that any damages suffered by Illumina are readily quantifiable and compensable. *Id.* at 26. Finally, BGI argues that Illumina has failed to establish an adequate causal nexus because its products have advantages over Illumina's products other than the accused features. *Id.* at 27.

BGI's arguments of irreparable harm are not supported by the law. It is undisputed that Illumina is currently the primary actor in the market, and BGI's commercial expansion into the United States would create essentially a two-player market. Sales made to BGI would almost certainly translate to lost revenue for Illumina. *See Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1151 (Fed. Cir. 2011) ("the existence of a two-player market may well serve as a substantial ground for *granting* an injunction—e.g., because it creates an inference that an infringing sale amounts to a lost sale for the patentee"). In addition, there is a high likelihood of price erosion. BGI admits that it competes with Illumina on price and touts its products as having a lower price point. Opp. 1-2. BGI also does not seriously dispute that in China, where it has already competed with Illumina, Illumina has had to lower its prices. *Id.* at 25-26. Although BGI suggests that sales in China are irrelevant to the U.S. market, it does not provide any substantive argument to distinguish the two markets. *Id.* at 24-25. I am persuaded by Illumina's position that evidence from another market in which Illumina and BGI have competed is probative of the potential impact of competition in the United States.

I also find that Illumina has established that it will suffer harm as a result of BGI's contacts with key opinion leaders ("KOLs"). Illumina argues that offering products on a no-cost basis to KOLs, which are highly influential in the market, will allow BGI to develop contacts, drive down price, and promote its products, generally at the expense of Illumina. Mot. I at 2. In its opposition, BGI does not address this argument. BGI's contacts with and offer of products to KOLs is the type of non-quantifiable harm that cannot be remedied by monetary damages. Providing no-cost exemplary products to influential leaders in the industry will damage Illumina by driving down price and eroding its market position. Moreover, BGI's argument that Illumina will not suffer reputational harm amounts to little more than a statement that because Illumina is instantiated in the market, its reputation cannot be impacted by a competitor's actions. Opp. 26. It provides no legal support for this argument, which I find unpersuasive.

BGI's arguments that damages could be readily quantified are further undermined by the nature of the market for the sequencers that it sells. Sequencers are expensive and a company can expect to sell less than 500 units in one year. Opp. at 25. In addition, Illumina uses long-term contracts and sole-source tenders. *Id.* at 26. Thus, the sale of even a few sequencers is significant, and one sale may entail significant reputational concerns with customers. In sum, the harm that Illumina has identified is of the type that courts frequently find weighs in favor of an injunction. *Mylan Institutional LLC v. Aurobindo Pharma Ltd.*, 857 F.3d 858, 872 (Fed. Cir. 2017) (irreparable harm where patentee will "suffer from lost sales, lost research and development, price erosion, and having to directly compete with an infringer"); *Douglas Dynamics, LLC v. Buyers Prod. Co.*, 717 F.3d 1336, 1345 (Fed. Cir. 2013) ("Where two companies are in competition against one another, the patentee suffers the harm—often irreparable—of being forced to compete against products that incorporate and infringe its own patented inventions.").

Lastly, Illumina has adequately demonstrated a causal nexus between the alleged harm and the alleged infringement. BGI does not seriously dispute that it is direct competitor of Illumina or that the driving feature of sales of sequencers is the ability to accurately sequence DNA. *See* Opp. 24; *see also Illumina II*, Dkt. No. 75-10 at 54:12-55:10. I am not persuaded by BGI's arguments that features other than those covered by Illumina's patents are the driving factor in sales of its products.

Therefore, Illumina has demonstrated that the threat of irreparable harm weighs in favor of granting its motion. *Qiagen*, 207 F. Supp. 3d at 1094 (finding that "Illumina has demonstrated a real risk that Qiagen could capture and redefine the market with its pirated technology" and that "[c]ompensation for lost sales will not adequately remedy the harm Qiagen could do to Illumina's business absent an injunction.").

III. BALANCE OF THE EQUITIES AND PUBLIC INTEREST

BGI contends that equity favors denying Illumina's motion because it has invested substantial research and development in its products, because Illumina is infringing its patent rights, and because an injunction would put local jobs at risk. Opp. 27-28. It asserts that the public interest weighs in favor of denying the injunction because its products provide meaningful

alternatives to the current genomic analysis on the market, will further the advancement of human genomic-based diagnostics, and will engender increased competition. *Id.* at 28-30. In response, Illumina points to the harms it faces if it must compete with infringing products and notes that BGI could continue its research, development, and marketing activities outside of the United States. Reply 17-20. Moreover, it states that its products have massively benefitted the public and that infringement does not benefit the public interest. *Id.* at 19-20.

I note that courts regularly find that a potential infringer's interest in entering the market pending outcome of patent litigation does not outweigh the plaintiff's interest in its patents. *See Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362–63 (Fed. Cir. 2008); *Pfizer, Inc. v. Teva Pharm., USA, Inc.*, 429 F.3d 1364, 1382 (Fed. Cir. 2005). This is so even where, as here, a new entrant to a market could benefit the public by bringing medically-important products to market. *Id.* Thus, BGI's arguments regarding the balance of equities and public interest are not strong. Moreover, Illumina has identified a serious risk of harm from BGI's potential infringement. *See Qiagen*, 207 F. Supp. 3d at 1094 (finding that balance of hardships and public interest weighed in favor of granting motion). Therefore, I find that the balance of equities and the public interest weigh in favor of enjoining BGI's infringing activities.

Although Illumina's potential infringement of BGI's patents is of serious concern, BGI has not provided any legal support for the position that the balance of hardships weighs in favor of a likely infringer when it has countersued for patent infringement. The merits of BGI's patent infringement allegations are not at issue in this motion. They do not change my determination that the balance of hardships and public interest weigh in favor of granting Illumina's motion.

IV. SCOPE OF THE PROPOSED INJUNCTION

BGI contends that Illumina's proposed injunction is overbroad, especially with respect to its standardMPS products, because it would enjoin ongoing research and development activities that pose no threat of harm to Illumina. Opp. 30. For the reasons discussed above, BGI's research and development activities, including no-cost trials with KOLs, harm Illumina. Moreover, Illumina has provided evidence that a key benefit of its accused products is for research purposes. *See* Reply 20. Finally, Illumina's allegations against BGI's standardMPS products, which BGI

seeks to use for research and development only, are particularly strong. BGI does not challenge the validity of the patents asserted in *Illumina I* —indeed, the validity of the '537 patent has been upheld numerous times. BGI also does not seriously contend that its standardMPS products infringe these patents. Therefore, BGI's research and development activities are appropriately the subject of an injunction.

However, I am persuaded by BGI's arguments that its sample preparation systems do not infringe the asserted patents. Opp. 30. Illumina alleges that the sample preparation systems contributorily infringe because they provide materials and apparatuses for practicing each patent claim. *See*, e.g., *Illumina II*, Dkt. No. 1 ¶¶ 53, 57, 62. BGI states that these systems "can be used with unaccused sequencing systems," and cites to expert testimony and marketing materials. Opp. 30. Illumina does not respond to this argument in its reply. Accordingly, Illumina has failed to adequately demonstrate infringement of such systems and they are not included in this injunction.[5]

CONCLUSION

For the above reasons, Illumina's motions for a preliminary injunction are GRANTED.

IT IS SO ORDERED.

Dated: June 13, 2020

William H. Orrick
United States District Judge

[5] I note that Illumina also alleges that some sample preparation systems are sold as part of infringing sequencer modules. *Illumina II*, Dkt. No. 1 ¶ 43. Such systems would infringe Illumina's patents and are enjoined.